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FILE 'CAPLUS' ENTERED AT 11:19:19 ON 07 FEB 2004

L1 2 S WO9901421/PN

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L3 1 S 197520-71-1/RN

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L4 1 S 219796-67-5/RN

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L5 11 S E4-E14

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L6 6 S L5

FILE 'EUROPATFULL, PATDPAFULL, PCTFULL, RDISCLOSURE, USPATFULL, USPAT2'

ENTERED AT 11:29:13 ON 07 FEB 2004

L7 18 S MEK(5A) INHIBITORS AND (WARNER(3A) LAMBERT OR PFIZER)

FILE 'CAPLUS' ENTERED AT 11:32:43 ON 07 FEB 2004

L8 3 S L6 AND PAIN



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#### **Brain Research**

Volume 566, Issues 1-2, 6 December 1991, Pages 95-102

doi:10.1016/0006-8993(91)91685-T (?) Cite or link using doi Copyright © 1991 Published by Elsevier Science B.V.

This Document

- ▶ Abstract
- Abstract + References
- PDF (1050 K)

### Research report

#### **Actions**

· E-mail Article

# Neurochemical studies on the mesolimbic circuitry of antinociception

O. P. Ma and J. S. Han

Neuroscience Research Center, Beijing Medical University, Beijing, People's Republic of China Accepted 16 July 1991.; Available online 7 March 2003.

## **Abstract**

Previous studies using the technique of microinjection into brain nuclei indicated that the periaqueductal gray (PAG), nucleus accumbens, habenula and amygdala play an essential role in pain modulation and that these nuclei possibly act through a 'mesolimbic neural loop' to exert an analgesic effect, in which Met-enkephalin (MEK) and  $\beta$ -endorphin ( $\beta$ -EP) have been implicated as the two major opioid peptides involved in antinociception. In the present study performed in rabbits, intracranial microinjection was supplemented with push-pull perfusion and radioimmunoassay to determine whether the release of enkephalins (ENK) and  $\beta$ -EP was increased in these nuclei when the putative neural circuit was activated by morphine administered into one of the nuclei. The results showed: (1) microinjection of morphine into the PAG increased the release of ENK and  $\beta$ -EP in the N. accumbens, and vice versa; (2) microinjection of morphine into the N. accumbens increased the release of ENK and  $\beta$ -EP in the amygdala, and vice versa; (3) morphine microinjected into the PAG caused an increase in the release of ENK and  $\beta$ -EP in the amygdala and vice versa, although the release of ENK in PAG was statistically not significant. These results indicate that PAG, N. accumbens and amygdala are connected in a network served by a positive feedback circuitry.

Author Keywords: Periaqueductal gray; Nucleus accumbens; Amygdala; Morphine; Enkephalin;  $\beta$ -Endorphin

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN

RN 219796-67-5 REGISTRY

CN Benzoic acid, 2,4-bis[(2-chloro-4-iodophenyl)amino]-3-fluoro-5-nitro-(9CI) (CA INDEX NAME)

OTHER NAMES:

CN 2,4-Bis(2-chloro-4-iodophenylamino)-3-fluoro-5-nitrobenzoic acid

FS 3D CONCORD

MF C19 H10 Cl2 F I2 N3 O4

SR CA

LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

- 6 REFERENCES IN FILE CA (1907 TO DATE)
- 6 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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INVENTOR(S):

L6 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:35363 CAPLUS

DOCUMENT NUMBER: 138:89582

TITLE: Preparation of 4-arylamino, 4-aryloxy, and 4-arylthio

diarylamines and derivatives as selective MEK

inhibitors for use as immunomodulators,

anti-inflammatory agents, and antiproliferative agents

Barrett, Stephen; Tecle, Haile

PATENT ASSIGNEE(S): Warner-Lambert Company, USA

SOURCE: U.S., 16 pp., Cont.-in-part of U.S. Ser. No. 462,319.

CODEN: USXXAM

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

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OTHER SOURCE(S): MARPAT 138:89582

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:63820 CAPLUS

DOCUMENT NUMBER: 134:131318

TITLE: Preparation of (phenylamino)benzenesulfonamides and

(phenylamino) benzamides as MEK inhibitors for the

treatment of chronic pain

INVENTOR(S):
Bridges, Alexander James; Booth, Richard John; Tecle,

Haile; Scaggs, Yvonne; Kaufman, Michael; Barrett, Stephen Douglas; Dixon, Alistair; Lee, Kevin; Pinnock,

Robert Denham

PATENT ASSIGNEE(S): Warner-Lambert Company, USA

SOURCE: PCT Int. Appl., 158 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent English

LANGUAGE:

FAMILY ACC. NUM. COUNT:

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OTHER SOURCE(S):
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ANSWER 3 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

2001:63819 CAPLUS

DOCUMENT NUMBER:

134:131317

TITLE:

Preparation of 2-phenylaminobenzamides and analogs as

MEK inhibitors for the treatment of chronic pain Dixon, Alistair; Lee, Kevin; Pinnock, Robert Denham

INVENTOR(S):

Warner-Lambert Company, USA

PATENT ASSIGNEE(S):

PCT Int. Appl., 132 pp.

SOURCE:

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

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OTHER SOURCE(S): MARPAT 134:131317

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ANSWER 4 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:
                   2001:63818 CAPLUS
DOCUMENT NUMBER:
                        134:131540
                        Preparation of (2-heterocyclylphenyl) (4-
TITLE:
                        iodophenyl) amines as MEK inhibitors for the treatment
                        of chronic pain
                        Barrett, Stephen Douglas; Bridges, Alexander James;
INVENTOR(S):
                        Tecle, Haile; Dixon, Alistair; Lee, Kevin; Pinnock,
                        Robert Denham; Zhang, Lu-Yan
PATENT ASSIGNEE(S):
                        Warner-Lambert Company, USA
                        PCT Int. Appl., 104 pp.
SOURCE:
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ACCESSION NUMBER:
                      2000:493498 CAPLUS
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TITLE:
                        Preparation of N-iodophenylanthranilates and analogs
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INVENTOR(S):
                        Barrett, Stephen Douglas; Tecle, Haile
PATENT ASSIGNEE(S):
                        Warner-Lambert Company, USA
                        PCT Int. Appl., 49 pp.
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ACCESSION NUMBER:
                       1999:48694 CAPLUS
DOCUMENT NUMBER:
                        130:124898
TITLE:
                        Preparation of 2-(4-bromo or 4-iodo
                        phenylamino) benzoic acid derivatives as MEK inhibitors
INVENTOR(S):
                        Barrett, Stephen Douglas; Bridges, Alexander James;
                        Cody, Donna Reynolds; Doherty, Annette Marian; Dudley,
                        David Thomas; Saltiel, Alan Robert; Schroeder, Mel
                        Conrad; Tecle, Haile
PATENT ASSIGNEE(S):
                        Warner-Lambert Company, USA
                        PCT Int. Appl., 67 pp.
SOURCE:
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DOCUMENT TYPE:
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LANGUAGE:
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OTHER SOURCE(S): MARPAT 130:124898

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                        Preparation of (phenylamino) benzenesulfonamides and
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                         (phenylamino) benzamides as MEK inhibitors for the
                         treatment of chronic pain
INVENTOR(S):
                        Bridges, Alexander James; Booth, Richard John; Tecle,
                        Haile; Scaggs, Yvonne; Kaufman, Michael; Barrett,
                        Stephen Douglas; Dixon, Alistair; Lee, Kevin; Pinnock,
                        Robert Denham
PATENT ASSIGNEE(S):
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SOURCE:
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TITLE:
                        Preparation of 2-phenylaminobenzamides and analogs as
                        MEK inhibitors for the treatment of chronic
INVENTOR(S):
                        Dixon, Alistair; Lee, Kevin; Pinnock, Robert Denham
PATENT ASSIGNEE(S):
                        Warner-Lambert Company, USA
SOURCE:
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PCT Int. Appl., 132 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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KIND DATE
                                 APPLICATION NO. DATE
    PATENT NO.
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                                       ______
                                      WO 2000-US18347 20000705
    WO 2001005392 A2
                         20010125
    WO 2001005392
                   A3
                         20010719
           AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ,
           EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT,
           LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR,
           TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
           DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,
           CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
                                    EP 2000-943383 20000705
                    A2 20020508
           AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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                         20030228
                                       ZA 2001-9907
                                                       20011130
    ZA 2001009907
                   Α
                                    US 1999-144292P P 19990716
PRIORITY APPLN. INFO.:
                                     WO 2000-US18347 W 20000705
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OTHER SOURCE(S): MARPAT 134:131317

L8 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:63818 CAPLUS

DOCUMENT NUMBER: 134:131540

TITLE: Preparation of (2-heterocyclylphenyl) (4-

iodophenyl) amines as MEK inhibitors for the treatment

of chronic pain

INVENTOR(S): Barrett, Stephen Douglas; Bridges, Alexander James;

Tecle, Haile; Dixon, Alistair; Lee, Kevin; Pinnock,

Robert Denham; Zhang, Lu-Yan

PATENT ASSIGNEE(S): Warner-Lambert Company, USA

SOURCE: PCT Int. Appl., 104 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

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APPLICATION NO. DATE
     PATENT NO. KIND DATE
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     WO 2001005391 A2
                            20010125
                                          WO 2000-US18346 20000705
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     WO 2001005391
                      A3
            AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ,
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                                          EP 2000-943382 20000705
     EP 1202732
                      A2 20020508
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL
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                                            ZA 2001-9903
                                                             20011130
                                         US 1999-144403P P 19990716
PRIORITY APPLN. INFO.:
                                         WO 2000-US18346 W 20000705
OTHER SOURCE(S): MARPAT 134:131540
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19/049, 762

L2 ANSWER 2 OF 2418 MEDLINE on STN ACCESSION NUMBER: 2003419470 MEDLINE

DOCUMENT NUMBER: 22839652 PubMed ID: 12959289

TITLE: Analgesic efficacy of non-steroidal antiinflammatory drugs in experimental pain

in humans.

AUTHOR: Walker J S; Arroyo J F; Nguyen T; Day R O

CORPORATE SOURCE: Department of Clinical Pharmacology and Toxicology, Garvan

Institute of Medical Research, St Vincent's Hospital, NSW

2010, Australia.

SOURCE: BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, (1993 Nov) 36 (5)

417-25.

Journal code: 7503323. ISSN: 0306-5251.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200309

ENTRY DATE: Entered STN: 20030909

Last Updated on STN: 20030918 Entered Medline: 20030917

The aim of this study was to establish a simple and reliable AB experimental pain model that could distinguish the analgesic effects of non-steroidal anti-inflammatory drug (NSAID) treatment from placebo in human volunteers. 2. The reproducibility and reliability over time of subject pain ratings was compared using cutaneous electrical stimuli applied to either the thenar eminence or the ear lobe at varying intensities and modes. Subjects were asked to respond firstly, when the stimulus became clearly sharp and painful ('first pain') and secondly, when the sensation became deep and burning and no further increase in stimulus intensity could be tolerated ('second pain'). 3. Constant voltage stimuli were found to be more reproducible than constant current stimuli. Both phasic (intermittent) and tonic (continuous) stimulation modalities produced 'first' and 'second pain' sensations. latter sensation was more reproducible, and was perceived as a burning pain which is akin to clinical pain. 4. Analgesics from the NSAID class were found to attenuate reliably only 'second pain' sensations. The analgesic effects of ibuprofen (ibuprofen vs placebo: 0.12 +/- 0.09 vs 0.02 +/- 0.07 volt h(-1), P = 0.03; 95% confidence interval fordifferences (CI): 0.03-0.18) and diflunisal (diflunisal vs placebo: 0.29 +/- 0.40 vs 0.005 +/- 0.27 volt h(-1), P = 0.0001; CI: 0.168-0.407), respectively, could be distinguished from placebo.

TI Analgesic efficacy of non-steroidal anti-inflammatory drugs in experimental pain in humans.

AB 1. The aim of this study was to establish a simple and reliable experimental pain model that could distinguish the analgesic effects of non-steroidal anti-inflammatory drug (NSAID) treatment from placebo in human volunteers. 2. The reproducibility and reliability over time of subject pain ratings was. . .